STATEMENT OF

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BEFORE THE HOUSE OF REPRESENTATIVES

COMMITTEE ON OVERSIGHT AND

GOVERNMENT REFORM

HEARING: "SAFE AND AFFORDABLE

BIOTECH DRUGS – THE NEED FOR A

GENERIC PATHWAY"

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Good morning Chairman Waxman and Members of the Committee. I want to thank you for the invitation and the opportunity to present to you this morning on this very important topic to our industry and for the general public. I am Ganesh Venkataraman, co-founder and Senior Vice President of Research at Momenta Pharmaceuticals, Inc. Momenta is a young biotechnology company, founded in 2001, and based in Cambridge, MA with core science and leadership from the Massachusetts Institute of Technology. I am pleased to come before you today to discuss the scientific issues behind the need to create an abbreviated regulatory approval process for both biosimilar (comparable, and non-interchangeable) and biogeneric (equivalent, and interchangeable) drugs.

As an American citizen, I care about this at both personal and professional levels. As a biotechnology company that specializes in the characterization of complex mixtures, such as the complex protein drugs highlighted by today's hearing, Momenta has a strong interest in ensuring that Congress acts this year to provide a viable regulatory pathway for bringing safe and effective biosimilar and biogeneric drugs to market. Not only do we have products in development that would be adversely affected by inaction, but there is a strong public policy imperative for increasing access to safe and effective medicines. Moreover, we believe our company's experience demonstrates that the science and technology are available today to enable generic versions of complex mixture products. Establishing a safe and effective pathway also has the potential to drive continued scientific innovation from companies like ours and others by creating a flexible framework which allows the U.S. Food and Drug Administration (FDA) to make approval decisions based on the highest scientific standards.

Mr. Chairman, my comments here today will be limited to the scientific issues around creating such a regulatory framework as science is my core area of expertise. I will leave comments regarding specific policy, regulatory, or legislative process issues to my esteemed other panelists.

Background

By way of introduction, let me provide some background on Momenta Pharmaceuticals as well as my own professional experience. Momenta has an R&D pipeline that is somewhat atypical for a biotechnology company in that it includes both complex generic as well as novel drug candidates. Our product development efforts leverage our core technology expertise which is focused on the characterization, or thorough qualitative and quantitative analysis, of complex mixture drugs. Momenta's complex generic portfolio includes four complex mixture drugs: a complex polysaccharide mixture drug, a complex peptide mixture drug, and two glycoprotein mixture drugs. We also have a novel drug discovery and development program, where our lead product candidate is a rationally engineered anticoagulant, which is currently in Phase I clinical trials.

Prior to joining Momenta, I was a member of the research faculty at the Massachusetts Institute for Technology (MIT), where I studied the biochemistry and biophysics of complex molecules with a focus on complex carbohydrates, or sugars. I am a chemical engineer by training, having received both my MS and PhD degrees at MIT, with specific expertise in bioprocess engineering, protein structural characterization, and analytic and quantitative methods for characterizing complex mixtures. While at MIT, I, along with my colleagues Robert Langer and Ram Sasisekharan (both tenured professors at MIT), developed a novel analytical technology platform targeted at characterizing complex mixtures. With this platform as our foundation, we founded Momenta Pharmaceuticals.

Our initial research at MIT focused on analyzing and engineering complex sugar mixtures in order to better understand the role they play in human disease and pharmaceutical medicines. Sugars are one of the fundamental building blocks of human biology as linear sugars coat every cell in the human body and affect critical cellular interactions as well as the regulation of multiple disease states. Moreover, many complex drugs, including the biologic drugs which are the focus of this legislation, are glycosylated (i.e., complex sugar structures are attached to the surface of the protein backbone). This glycosylation adds significantly to a molecule's structural complexity and affects many of its biological and clinical attributes.

The presence or absence, and the degree of glycosylation (i.e., how many sugar structures are attached to the protein) is a frequent delineation between simpler and more complex protein products.

While sugars' role in biology has been well documented in scientific literature, advances in biologics have been impeded by a lack of understanding of the chemical structures of these heterogenous molecules. Specific to this debate, the inability to thoroughly characterize complex molecules has been cited frequently as a barrier for creating a pathway for generic biologics. Momenta is developing the analytical technology platform necessary to make this type of characterization a reality. Our goal in this debate is to highlight the latest innovations in science and the potential applicability of recent technological advances to help unlock the challenge of creating biogeneric and biosimilar versions of biotechnology products.

Introduction

We believe that any regulatory framework that is established has to be flexible and provide for the approval of both biosimilar and biogeneric products. There is an opportunity to drive continued scientific innovation by creating a forward-looking regulatory system, which balances the respective roles that characterization, preclinical, human clinical, and other scientific data should play in the approval of biosimilar and biogeneric products.

In addition, the FDA has to have the opportunity to make decisions around interchangeability based on the science presented to them. Interchangeability refers to specific designations provided by the FDA which enables pharmacists and other medical professionals to substitute one product for another. Currently, most traditional generic products are interchangeable with their branded counterparts and provide equivalent therapies at reduced cost. While interchangeability may not be possible for most biologics today, it is well within reach in the near term for a number of products. It is absolutely essential that legislation enable a regulatory pathway which provides for interchangeability, which will maximize needed and significant healthcare savings so important to patients. If legislation does not allow such a

pathway today, scientific innovation from technology companies like ours and many others will be stifled. The incentive to innovate will simply not be there.

I will focus my specific comments today around 5 major topics which have been consistently raised in different forums. In my discussion, I hope to highlight the state of science today and counter some of the rhetoric that has been posed by opponents of a proposed abbreviated regulatory pathway for generic biologics. These 5 issues are:

1. Product Characterization:
    - Myth: Complex biologic products can never be fully characterized.
    - Response: Analytical technologies exist today and are already being used to enable thorough characterization of complex mixture products.
2. Process Characterization:
    - Myth: Generic companies will never be able to develop the critical knowledge and strict control of the manufacturing process necessary to reproducibly make biologic drugs with the same quality as the branded companies.
    - Response: Analytical technologies can enable a thorough understanding and control of the manufacturing process to produce high quality complex mixture products.
3. Clinical Trials:
    - Myth: Full scale clinical trials must be required for approval in all cases.
    - Response: The extent of clinical trial data required for the approval of a biosimilar or biogeneric complex product should be determined by the FDA on a product-by-product basis. In general, it is inversely related to the level of process and product characterization that is available. This standard would be consistent with the current approach taken by FDA when an innovator makes manufacturing changes to a novel biologic product.
4. Interchangeability:
    - Myth: Biologic drugs can never be interchangeable.
    - Response: Either through thorough characterization, or through the appropriate combination of characterization and clinical trials, it is possible for complex

biologic products to be equivalent and interchangeable with the innovator product.

5. Patient Safety and Product Quality:
    - Myth: Patient Safety and Product Quality will be jeopardized.
    - Response: By holding the industry to the highest scientific standards and relying on the experience and expertise of FDA's scientific staff (which review, approve, and oversee the marketing of innovator, biogeneric and biosimilar products), patient safety and product quality will not be compromised.

I would like to provide my scientific perspective on each of these issues in more detail, based on my experience at MIT, as well as work which is actively ongoing at Momenta. We, like others, are focused on achieving a better understanding of these complex biologics, what they are and how they are produced, to enable the development and commercialization of the highest quality biogeneric and biosimilar products needed by the public today and in the future.

Myth #1 – Complex biologic products can never be fully characterized.

Definition of Complex Mixture Drugs: First, we should agree on the definition of a complex mixture drug. We are most familiar today with small molecule drugs, which exist as simple chemical structures, that are synthetically derived. These small molecule drugs can be chemically characterized and are readily manufactured through comparatively simple chemical synthesis. Complex mixture drugs, in stark contrast, are much larger, heterogenous mixtures, consisting of many structurally unique molecules. These unique molecules differ in their chemical structure and abundance within a mixture, are all biologically active, and dictate a drug's overall physiological and clinical profile. While there are many complex mixture drugs, the most common are the biologic drugs (i.e., therapeutic proteins, which are produced by living cells and organisms), which is the focus of this hearing.

Biologic Drugs Vary in Complexity: It is important to note that not all biologic products are the same. While each consists of multiple unique proteins, their complexity is also dictated by the number and type of glycosylation sites (i.e., how many sugar structures are attached to the surface of the protein backbone). Human growth hormone, for example, is a non-glycosylated protein (i.e., there are no sugars attached to the protein backbone). In contrast, interferon beta has one glycosylation site, whereas erythropoietin has four glycosylation sites. When we begin to discuss the challenges of characterizing these complex biologic mixtures, we must keep in mind this *continuum of complexity*. While characterization challenges exist for the more complex biologic products, analytical technologies are here today to enable the thorough characterization of some of the less complex biologic drugs.

Low Molecular Weight Heparins – A Case Study: I would like to review our experience with low molecular weight heparins (LMWHs), which I feel will highlight how far science has advanced and also help you understand where science is moving in this field. This class of compounds are anti-coagulants, and include marketed products today such as Lovenox®, Fragmin®, and Innohep®, all of which we have worked on in our laboratories at Momenta.

LMWHs are commonly used in the treatment and prevention of Deep Vein Thrombosis, and the treatment and management of Acute Coronary Syndromes. LMWHs are derived from pig intestines, which are carefully purified and treated (following a number of key manufacturing process steps) to produce the final product. LMWHs are complex heterogenous mixtures of hundreds of different unique molecules. These molecules are linear "sugar" chains, which vary in length and also in structural complexity (i.e., the structure and arrangement of the different sugar building blocks). In order to produce an equivalent version of any one of these LMWHs, we have to develop an analytical technology platform which would allow us to thoroughly characterize the innovator products. We have successfully developed and fine tuned such an analytical approach to enable the thorough characterization of these complex mixtures. This approach requires multiple analytical methods and an extensive bioinformatics integration of the resulting data sets, and allows us to structurally identify and quantify the various molecules in the mixture, fully capturing the micro- and macro-heterogeneity which dictates overall physiological profile and clinical outcome in patients. By characterizing

multiple samples of a given LMWH product, we are also able to understand and quantify the variability inherent in the innovator product, as a result of the manufacturing process. This allows us to set the appropriate "goal posts" (or equivalence window) which we can target to reproducibly make an equivalent version of the innovator product.

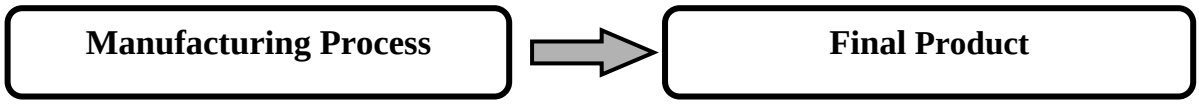
Biologics, which are produced by living cells, represent a new and different challenge. However, biologic drugs are also mixtures of many unique molecules, which vary in structure and abundance within the final mixture. Whereas LMWH products are mixtures of linear sugar chain molecules, biologic drugs are mixtures of protein-sugar molecules. The analytical approach we have applied to LMWHs can and is now being applied to these complex biologic drugs today. Analytical technologies are already here today to characterize the less complex biologic drugs, and approaches like ours and others are actively being developed which will make thorough characterization of the more complex biologic drugs a reality in the near future. While not possible for LMWHs only a few years ago, science has now advanced to allow for the thorough characterization of these complex mixture drugs. Thorough characterization of more complex biologic drugs will thus come sooner than we think, as scientific innovation continues to advance rapidly in this field.

Myth #2 – Generic companies will never be able to develop the critical knowledge and strict control of the manufacturing process necessary to reproducibly make biologic drugs with the same quality as the branded companies.

Understanding the Manufacturing Process: As I discussed earlier, biologic drugs are produced by complex, living organisms. This brings an obvious added level of complexity to the manufacturing process over the simpler chemical manufacturing processes which are practiced for small molecule drugs. However, it is important to acknowledge that the manufacturing process for biologic drugs does not occur in a random, or uncontrolled "system". First, a cell produces a certain protein. Then, the cell modifies the protein in many ways, for example by adding selected complex sugar molecules to the protein backbone, which can produce changes in conformational structure and design. These latter changes are often called "post-translational modifications". Thus, these living cells are actually highly

specialized systems which in a careful, and very controlled manner, produce the various molecules that constitute the final biologic mixture. As practiced currently by the innovator, analytical technologies can be utilized to understand the manufacturing process and its intricate relationship with the final product. It is possible, and will be absolutely critical that the generic company and contract manufacturers also build and maintain this same level of process knowledge. With tools such as those that Momenta and others are developing, even innovator companies may be able to better control their manufacturing process in the future.

Low Molecular Weight Heparins – A Case Study: Again, I would like to use our internal work with LMWHs to highlight the value of building a process-product relationship for a complex mixture drug. As I discussed earlier, LMWHs are derived from pig intestines, via cells which biosynthetically produce the heparin starting material needed for the manufacturing process. As we are able to fully characterize a given LMWH product and define its inherent variability, we can determine the "goal posts" which we need to target to ensure we can make an equivalent version of a LMWH product. With such an analytical framework in place, we can carefully study and understand the impact of the starting material (the pig intestines or porcine mucosa, and the final purified heparin), and the critical steps in the manufacturing process. Following a careful, step-by-step approach, we can reverse engineer the manufacturing process, build a strong knowledge and experience base with our process, and determine the critical elements we need to control to ensure that we can reproducibly make an equivalent version of a LMWH product. In simple terms, we need to understand which "dials" are important to turn in the manufacturing process, and appropriately adjust and control these "dials" to ensure a quality product time and time again. The figure below highlights the critical relationship between process and product.



Process Characterization
- *process knowledge and understanding of starting material and process parameters*
- *process engineering*
- *process quality and control*

Product Characterization
- *identify and quantify the molecules which comprise the mixture*
- *define variability in innovator product*
- *determine "equivalence window" for complex generic product*

This same approach can be applied to biologic products. There is a certain predictability to how cells produce the protein backbone and modify this backbone to produce the final product. This is not a random, uncontrolled system. Scientific advances in analytical technologies, available to the generic as well as the innovator companies, make this type of process knowledge and understanding a reality for some simpler biologics today and will make it possible for other, more complex biologics in the near future.

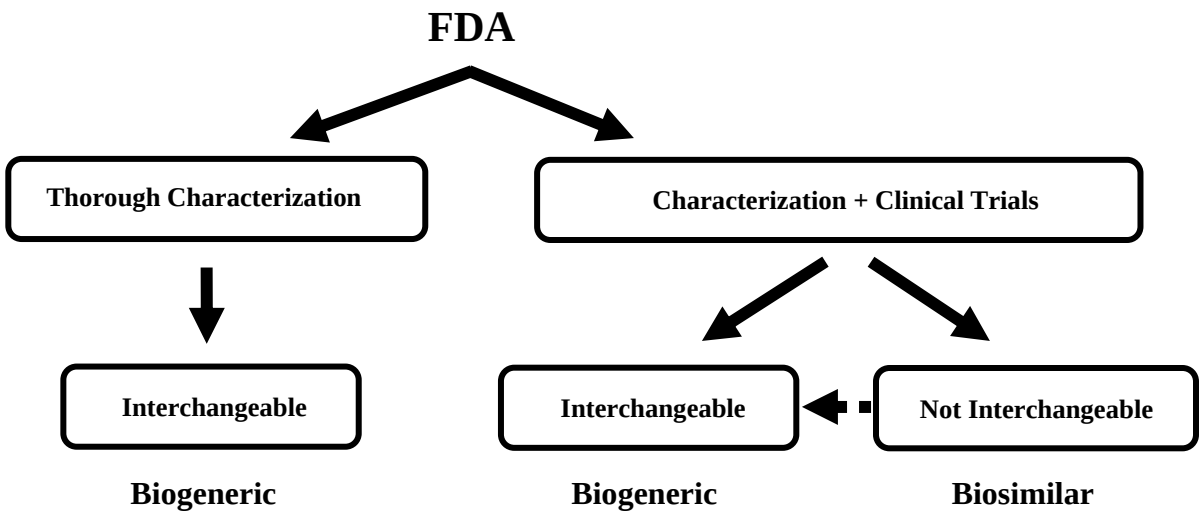
Myth #3: Full scale clinical trials must be required for approval in all cases.

Here again it is important to acknowledge the continuum of complexity of biologic drugs. The level of characterization data will allow the FDA to determine the extent of clinical testing which will be necessary for approval. While FDA may require full scale clinical trials for approval of some biologic products, significantly reduced clinical testing requirements (i.e., smaller scale clinical studies assessing bioequivalence, immunogenicity, or more targeted clinical endpoints) will be required for the approval of other biologic products due to the increased level of characterization data which is provided. We are establishing the feasibility of, and are working toward the characterization tools which will demonstrate equivalence to innovator product and manufacturing control. This thorough characterization will ensure the biologic products produced can be relied on to produce the same clinical result as the innovators product in a given patient without the need for extensive clinical trials. We believe the FDA is well equipped to work with applicants to determine the degree of testing necessary

and believe any legislation should enable a substitutable pathway and leave the definition of characterization and trial requirements to the FDA.

Myth #4: Biologic Drugs can never be interchangeable.

FDA must have the freedom to evaluate each application and make the appropriate determination of comparability versus interchangeability. As the diagram below presents, we support the creation of both a biogeneric and biosimilar pathway.



We see three distinct regulatory pathways to enable the approval of biologic products. In the near term, due to the complexity of most of these biologics, most applicants will pursue a biosimilar regulatory path, based on a combination of characterization and clinical data. Particularly for less complex biologic drugs, and with the continued advancement of analytical technologies, some applicants will also pursue a biogeneric regulatory path by providing sufficient characterization data, likely coupled with reduced clinical data requirements, to clearly demonstrate that its product will reliably produce the same clinical effects as the innovator drug in a given patient. Finally, while I recognize that thorough characterization is only possible today for the less complex mixture drugs, we feel it is critically important that a pathway which relies on thorough characterization, analogous to what we have today for small molecule drugs, also be authorized to drive continued scientific

innovation in this field. It is via the two biogeneric legislatively authorized paths, where the significant cost savings to the American public will become a reality.

Myth #5: Patient Safety and Product Quality will be jeopardized

The final issue I would like to highlight is the need to hold the entire industry, branded and generic alike, to the highest quality and safety standards as they bring new products to market. We believe that the standards for generics and novel drugs should be comparable and seek parity among the approval systems for these products. To this end, we encourage the development of a regulatory framework that provides FDA with discretion to produce appropriate guidance based on its own understanding of what is scientifically reasonable. We have collectively entrusted FDA with the authority to approve complex biologic products for years. We will rely on this same scientific team and expertise at FDA to make the appropriate science-based decisions for biogeneric and biosimilar approvals. With the appropriate application of the latest technology, patient safety and product quality will not be compromised.

Summary

In conclusion, I would like to restate our core beliefs on this issue.

- The tools for characterization of complex drugs are at hand. It is already possible to thoroughly characterize complex mixture products.
- Today's technologies can ensure reproducible and well controlled manufacturing processes which can deliver safe and reliable products in the hands of competent biologic manufacturers.
- Bioequivalence and safety for biosimilar and biogeneric products can be demonstrated through complementary sets of characterization analytics and where necessary, limited clinical trial data.
- Legislation that provides for interchangeable biogenerics is essential to provide the incentives for the industry to continue to invest and innovate in needed characterization and process control technologies. This is the single best way to

ensure the competition necessary to deliver these drugs safely and cost effectively to the patients that most need them.

- We should rely on FDA, which has been approving complex biologics for years, to ensure the highest quality and safety standards going forward.

Mr. Chairman, I want to thank you again for your leadership in raising attention to the need for a timely and responsive legislatively authorized pathway, which has the potential to make biogeneric and biosimilar medications a reality in this country. We believe it is critical for all of us that such a framework be created that is forward looking and enables science to drive our future direction. I hope that my perspectives have been instructive to this debate. I am confident that these efforts under your leadership will be a key contributor to increasing access to safe, effective, and affordable medications to patients in need.

I thank you again for the opportunity to submit testimony today and look forward to answering any questions you may have.